Remarks

A. Status of Claims

No claims have been amended. Claims 21-30 remain pending.

B. The Claims Are Enabled

Claims 21-30 are rejected under 35 U.S.C. §112, first paragraph for allegedly lacking enablement. Applicant respectfully disagrees and asks that this rejection be withdrawn.

1. The Enablement Rejection is Not Proper Because Yiv Does Not Involve an Identical Process

The Examiner correctly notes that U.S. Patent No. 6.245,349 ("Yiv") discloses techniques that generate a product that is **not a solid**. Office Action, page 2. The Examiner also correctly notes that the present claims recite the formation of a **solid** nanoparticle. *Id.* In concluding that the present claims are not enabled, the Examiner relies on the following premise: Yiv involves "the same components being used and manufactured in an identical way to that of applicant." *Id.* Based on this premise, the Examiner argues that the practice of the present claims cannot result in a **solid** nanoparticle because Yiv allegedly teaches that a **non-solid** product should result. *Id.*; Office Action, pages 5-6.

The premise relied on by the Examiner is incorrect, and the present enablement rejection is not proper. Yiv does not involve a process that is even similar to that described by the present claims, much less "identical." In the previous Response, Applicant explained numerous patentable and significant distinctions between the disclosure of Yiv and the subject matter of the claims, which are summarized and supplemented below.

Claim 21 recites a microemulsion that includes a liquid nanoparticle matrix material **formed by heating a solid matrix material until melted**. Yiv nowhere discloses or suggests this feature, as previously confirmed via telephone interview with the Examiner. Instead, Yiv

produces oil-in-water microemulsions by **diluting different materials that are liquid** at room temperature. Yiv, column 6, lines 41-65; Example 1, columns 9-10. In all Yiv Examples (Examples 1-9), Captex 200 or Captex 300 is used as the liquid oil phase. Captex 200 and Captex 300 are liquids at room temperature. *See* Product Descriptions for Captex 200 and Captex 300 from Abitec Corporation, Exhibit 1. Now, however, the Examiner points to Yiv at column 4, lines 35-44 to assert that Yiv involves heating a solid until melted. Office Action, page 3, paragraph 2. This passage does not support the Examiner's position.

At column 4, lines 35-44, Yiv explains that if the concentrated drug delivery system is "very viscous" at room temperature (due to a high drug concentration), one can warm the system so that it will mix better with a diluent. It is well known to those of ordinary skill in the art that heating a viscous liquid can cause the liquid to become less viscous and thus easier to mix. *See, e.g.*, 20th Edition Remington: The Science and Practice of Pharmacy (2000), pages 336-338, Exhibit 2. The variation of viscosity with temperature is described by the well known Arrhenius equation. *Id.* at page 338. The term "viscous" describes **liquids**, and the cited Yiv passage is therefore directed to a situation in which one warms a high-drug-concentration liquid to reduce its viscosity so that better mixing with a diluent can be achieved. *See, e.g.*, Hawley's Condensed Chemical Dictionary (1993) (defining "viscosity" in relation to fluids or liquids), Exhibit 3. The mixing with the diluent, in turn, forms a liquid-in-liquid microemulsion. Yiv, column 4, lines 31-34 and 40-42. Nowhere does the Yiv passage cited by the Examiner disclose or suggest a liquid nanoparticle matrix material formed by heating a solid matrix material until melted—again, what is disclosed is the warming of a viscous liquid to generate a less-viscous liquid that can then be diluted to form a microemulsion.

Yiv also does not disclose or suggest making the recited oil-in-water microemulsion **by heating**, as required by claim 21, Yiv instead forms an oil-in-water microemulsion by a **dilution process of adding one liquid to another**: "The concentrated drug delivery compositions can be diluted with an aqueous fluid to form an oil-in-water microemulsion composition." Yiv, Abstract; column 2, lines 49-52. Yiv mentions a heating or warming step only for the purpose of dissolving a drug (Yiv, Example 3, column 11; Example 7, column 13), to reduce viscosity (Yiv, column 4, lines 34-39; column 15, lines 14-18, discussed above) or to dissolve phospholipids in a propylene glycol solution (column 14, lines 5-8; Figure 1).

Yiv also does not disclose or suggest **cooling** the recited microemulsion **to form a nanoparticle**, much less the recited **solid nanoparticle**. Yiv uses the term "nanoparticles" to refer to the oil-in-water microemulsions themselves, which are liquid-in-liquid systems formed by a dilution process. Yiv, column 5, lines 20-29; column 4, lines 31-34 and lines 40-42. The Examiner too has acknowledged that Yiv is not directed to generating a solid. Office Action, page 2.

In view of these stark differences, it is clear that Yiv does not teach an "identical" or even similar process to the subject matter of the claims. Therefore, there is no basis to argue that the practice of the present claims would result in the liquid microemulsion product described by Yiv. Making an oil-in-water microemulsion **by heating**, and **cooling** the microemulsion to form a **solid** nanoparticle are not contemplated by Yiv, and practice of the claimed steps result in an end-product different than Yiv: a solid nanoparticle instead of a liquid-in-liquid system. The only premise on which the current enablement rejection is based—Yiv being identical to the claims—is faulty, and no prima facie case for lack of enablement has been established. M.P.E.P. §2164.04 ("In order to make a rejection, the examiner has the initial burden to establish a

reasonable basis to question the enablement provided for the claimed invention."); *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976) (noting that the PTO must provide reasons supported by the record as a whole why the specification is not enabling); *In re Strahilevitz*, 668 F.2d. 1229, 1232 (CCPA 1982) (noting that, to meet the burden of proof, the Examiner must advance acceptable reasoning inconsistent with enablement). Applicant requests removal of the enablement rejection.

2. The Specification Teaches How To Make And Use the Claimed Solid Nanoparticles

The Examiner argues that the "process by which a solid is obtained ... is not enabled by the disclosure." Office Action, page 2. Applicant respectfully disagrees and refers the Examiner to the specification and the Declaration attached as Exhibit 4.

The claims (*e.g.*, Claim 21) and the specification at least at pages 20-21 and within Examples 6, 8, 9, and 13 (pages 30-33 and 35) disclose how to obtain solid nanoparticles. The Office has not explained why it doubts the truth or accuracy of any of this material in the specification, so the present rejection is not supported and should be withdrawn. M.P.E.P. §2164.04 (noting that "it is incumbent upon the Patent Office...to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.") (quoting *In re Marzocchi*, 439 F.2d 220, 224, (CCPA 1971)); *In re Marzocchi*, 439 F.2d 220, 223-24 (CCPA. 1971) ("In examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has 'acceptable evidence or reasoning' to suggest otherwise.").

a. Dr. Mumper's Declaration Rebuts the Current Enablement Rejection

Additional support for the enablement of the claims, and particularly enablement with respect to the formation of solid nanoparticles (as raised by the Examiner) is found in the Declaration at Exhibit 4.

In the Declaration, inventor Dr. Russell Mumper testifies that when exemplary procedures of the present application are followed consistent with the language of the claimed invention, solid nanoparticles are formed. Exhibit 4, ¶3.

Behind Tab A of the Declaration are results from experiments Dr. Mumper conducted, showing the formation of solid nanoparticles made in accordance with exemplary techniques consistent with the language of the claimed invention. Exhibit 4, ¶4. The results include seven figures (Figures 1-7). *Id.* Figure 1 shows the thermal analysis of nanoparticle components and nanoparticles using Differential Scanning Calorimetry (DSC). *Id.* Figure 2 is an image of the nanoparticles using a Transmission Electron Microscope (TEM). *Id.* Figures 3-7 are images of the nanoparticles taken using a high resolution field emission Scanning-Transmission Electron Microscope (STEM) operating in both TEM and STEM mode. *Id.* This type of STEM imaging uses z-contrast and creates an imaging signal that is proportional to the atomic number squared in the ideal case. *Id.* An Energy Dispersive X-ray Spectroscopy (EDS) profile is also included in Figure 7. *Id.* The STEM/EDS technique allows one to scan into a solid material and determine where an element is located. *Id.*

Referring to the figures of Tab A of the Declaration, it is evident that the pictured nanoparticles are solid for at least three reasons. Exhibit 4, ¶5. First, the DSC profile of the nanoparticles (Figure 1.3) shows a single endothermic peak at ~ 90° C demonstrating that the nanoparticles have a distinct and unique melting point and are therefore a solid. *Id.* Second, the TEM methods that were used to generate Figures 2-7 required the nanoparticle suspension to be

dried (water removed) on a substrate for suitable for TEM analysis. *Id.* After drying, distinct solid nanoparticles are observed (Figures 2-7). *Id.* In contrast, the drying of an oil-in-water microemulsion (a liquid-in-liquid) would result in a heterogeneous mass of coalesced oil deposited on the substrate. *Id.* In fact, for such a liquid system, Freeze-Fracture TEM (FF-TEM) would have to be employed to first freeze the system using low temperatures so that distortions associated with the removal of water can be avoided. *Id.* FF-TEM was not required for the imaging of the pictured nanoparticles because they are solid. *Id.* Third, as shown by X-ray Spectroscopy, Holmium (an element Dr. Mumper incorporated in the nanoparticles) is uniformly present in the pictured nanoparticle in a punctate manner. (Figures 4-7). *Id.* The Energy Dispersive X-ray Spectroscopy profile in Figure 7 illustrates that Holmium is present uniformly throughout the solid nanoparticle when the nanoparticle is scanned along its diameter. *Id.*

The solid nanoparticles discussed in the Declaration were made in accordance with exemplary techniques consistent with the language of Claim 21 and described at pages 20-21 of the specification and in Examples 6, 8, 9, and 13 of the specification (found at pages 30-33 and 35). Exhibit 4, ¶6.

For Figure 1 of Tab A of the Declaration, the solid nanoparticles were made by first melting emulsifying wax at 55° C. Exhibit 4, ¶7. Seven hundred μL of water was added into the melted wax and stirred using a magnetic mixer until a homogenous milky suspension was obtained. *Id.* Then, 0.3 mL of cetyltrimethyl ammonium bromide (CTAB) solution (50 mM) was added into the homogenate while stirring to obtain a clear microemulsion at 55° C. *Id.* Solid nanoparticles were then formed by cooling this warm microemulsion to room temperature, while stirring, in the same container. *Id.*

For Figure 2 of Tab A of the Declaration, the solid nanoparticles were made by weighing 2 mg of emulsifying wax into a 7-mL screwed capped glass vial. Exhibit 4, ¶8. The emulsifying wax was melted at 55° C. *Id.* To the melted emulsifying wax, 30 µL of 100 mM Brij 78 surfactant solution was added. *Id.* Next, water was added under magnetic stirring to prepare the oil-in-water microemulsion at 55° C with a final volume of 1000 µl. *Id.* Finally, solid nanoparticles were prepared directly from the warm microemulsion by cooling of the undiluted oil-in-water microemulsion at 55° C to room temperature, while stirring. *Id.*

For Figures 3-7 of Tab A of the Declaration, the solid nanoparticles were made using the following method. Exhibit 4, ¶9. In a 7-mL glass vial containing a 1 cm magnetic stir bar, two (2) milligrams of emulsifying wax was melted at 65° C to produce a liquid nanoparticle matrix material. *Id.* Next, 4.6 mg of Brij 78 surfactant was added. *Id.* Next, 0.5 mg Holmium-acetylacetonate (Ho-AcAc) was dissolved into the melted mixture of emulsifying wax and Brij 78. *Id.* One mL of water was added, and the mixture was heated for 15 minutes at 65° C while stirring with a magnetic mixer to make an oil-in-water microemulsion. *Id.* Finally, the oil-in-water microemulsion was then cooled to room temperature while stirring to form a solid nanoparticle with entrapped Ho-AcAc. *Id.*

It is evident that when nanoparticles are made according to exemplary techniques described in the present application and consistent with the language of the claimed invention, those nanoparticles are solid. Exhibit 4, ¶10.

In view of the specification and/or this Declaration, no reasonable argument can be advanced to support the current enablement rejection. Applicant requests that the rejection be withdrawn.

C. **The Claims Are Not Anticipated by Yiv**

Claims 21-23, 25-27, and 30 are rejected under 35 U.S.C. §102 for allegedly being anticipated by Yiv. Applicant respectfully disagrees and asks that this rejection be withdrawn.

Each claim requires the formation of a **solid nanoparticle** by a particular, recited process. Yiv cannot anticipate the claims because, as acknowledge by the Examiner, Yiv is not directed to the formation of a solid product. Office Action, page 2. In fact, the entire thrust of the present enablement rejection, now rebutted, is that Yiv's process results in a **non-solid** product, while the present claims require a **solid**. *Id.* Because Yiv lacks an explicit element of the claims, there can be no anticipation, and Applicant requests removal of this rejection.

Yiv also does not anticipate the claims for the numerous, independent reasons provided above in Section B.1. For at least those reasons as well, the present anticipation rejection should be withdrawn.

D. **The Claims Are Not Rendered Obvious by Yiv**

Claims 24, 28, and 29 are rejected under 35 U.S.C. §103 for allegedly being obvious in view of Yiv. Applicant respectfully disagrees and asks that this rejection be withdrawn. By fashioning this rejection as one of obviousness, the Examiner implicitly acknowledges that Yiv does not disclose elements of claims 24, 28, and 29 but yet does not provide any citation to evidence that would cure such deficiencies. Instead, the Examiner suggests that any subject matter concerning optimization or concentrations is *per se* not inventive. Office Action, page 5. Applicant respectfully disagrees with the Examiner and submits that the caselaw is not supportive of the Office's position. No evidence supports the current obviousness rejection, no prima facie case has been established, and the current rejection should therefore be withdrawn.

Additionally, claims 24, 28, and 29 are all dependent from claim 21, which is allowable as explained above. For this reason as well, the current obviousness rejection is not sustainable.

E. Conclusion

Applicant believes that this Submission fully responds to all outstanding matters for this application. Applicant respectfully requests that the rejections of all claims be withdrawn so the claims may swiftly pass to issuance. Please contact the undersigned attorney at 512-536-3018 with any questions.

Respectfully submitted,

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DATE: September 28, 2005

Captex® 200

CAS Number: 68583-51-7* EINECS Number: 271-516-3
INCI name: Propylene Glycol Dicaprylate/Dicaprate

Synonyms:

Decanoic Acid, Mixed Diesters with Octanoic Acid and Propylene Glycol

Product Description:

CAPTEX 200 is an ester manufactured by the esterification of fractionated coconut fatty acids (mainly caprylic and capric) with propylene glycol. It is fully refined and deodorized. It is miscible with most organic solvents including 95% ethanol. The low viscosity, excellent lubricity and relatively non-oily character of **CAPTEX 200** makes it ideally suited for a variety of pharmaceutical, nutritional, personal care and cosmetic applications. **CAPTEX 200** carries Kosher certification and has excellent stability, low irritation, bland taste and odor. Propylene glycol mono- and diesters of fats and fatty acids are FDA approved according to 21 CFR § 172.856.

Specifications:

Specification	Limit	Test Method
Odor	Bland	Sensory
Acid Value	0.1 max	[1]AOCS Cd 3d-63
Color APHA	100	AOCS Td 1b-64
Saponification Value	315-335	AOCS Cd 3.25
Iodine Value	1.0 max.	[2]USP <401>
Moisture, KF	0.1 % max	AOCS Ca 2e-84

[1]AOCS: American Oil Chemists' Society. [2]Current United States Pharmacopeia.

Typical Properties:

Appearance/Form	Clear Liquid	Visual
Specific Gravity @ 77°F (25°C)	0.92 - 0.96	[2]USP
Viscosity @ 77°F (25°C)	8	Brookfield
Cloud Point	5°F or less	AOCS Cc 6 - 25

[2]United States Pharmacopeia.

Typical Fatty Acid Distribution by GLC:

6:0 Caproic acid.....1.0–5.0%
8:0 Caprylic acid.....60.0-70.0%
10:0 Capric acid.....20.0-30.0%
12:0 Lauric acid.....1.0%

501 West First Avenue, Columbus, Ohio 43215 **Phone: 614-429-6464 Fax: 614-299-8279**
email: www.abiteccorp.com

Captex® 200

Personal Care Applications:

- Skin conditioning agent
- Emollient used in liquid foundations and color cosmetics
- Low viscosity, excellent lubricity, relatively non-oily after feel
- Excellent stability, low irritation, fully refined and deoderized
- Use level: 0.5—10.0% (w/w)

Nutritional Applications :

- Carrier (vehicle)
- Solubilizer
- Energy Source
- Viscosity Modifier

Shelf-Life:

Retest and requalify 2 years from the date of manufacture.

Storage:

Store in a dry place at ambient temperature.

Standard Package:

Tank wagons, 425 lb. (193 kg) drums or 50 lb. (22.7 kg) pails

Captex® 300

CAS Number: 65381-09-1, 73398-61-5 EINECS Number:265-724-3, 277-452-2
INCI name: Caprylic/Capric Triglyceride

Synonyms:

Medium Chain Triglycerides (MCT)
Glycerol Caprylate Caprate
Octanoic/ Decanoic Acid, Triglycerides

Product Description:

Captex 300 (also known as medium-chain triglycerides or, MCT's) is manufactured by the esterification of fractionated coconut oil fatty acids (mainly, caprylic and capric) and glycerin. **Captex 300** is prepared from food-grade, vegetable oil raw materials. It is fully refined and deodorized and is miscible with most organic solvents including 95% ethanol.

Specifications:

Specification	Limit	Test Method
Appearance/Form	Light yellow/Clear Liquid	Visual
Odor	Bland	Sensory
Acid Value	0.1 max	[1]AOCS Cd 3d-63
Color, APHA	100 max	Tintometer PFX 990
Saponification Value	335-360	AOCS Cd 3a-94
Moisture, KF	0.1 % max	AOCS Ca 2e-84

[1]AOCS: American Oil Chemists' Society.

Typical Properties:

Specific Gravity @ 77°F (25°C)	0.92 - 0.96	[2]USP
Viscosity, cP @ 77°F (25°C)	20 - 25	Brookfield
Cloud Point	28°F or less	AOCS Cc 6-25

[2]USP: United States Pharmacopeia.

Typical Fatty Acid Distribution by GLC:

6:0 Caproic Acid..... 6.0% max.
8:0 Caprylic Acid..... 55.5-85.0%
10:0 Capric Acid..... 15.0-40.0%
12:0 Lauric Acid..... 4.0% max.

501 West First Avenue, Columbus, Ohio 43215 **Phone: 614-429-6464 Fax: 614-299-8279**
email: www.abiteccorp.com

Captex® 300

Toxicology Information:

Test	Result
Oral LD_{50}:	> 36 ml/kg in rats
	> 25 ml/kg in mice
Draize Skin Test:	No or slight irritation potential
Buehler Sensitization:	No reaction
Human Skin Patch Tests (undiluted sample) :	No perceptible skin alteration
Human Mucous Membrane Tests (undiluted sample) :	No eye irritation

Personal Care Applications:

- Skin conditioning agent, occlusive agent, solubilizer, leaves a light silky after-feel
- Recommended for use in skin care products, lipsticks, and foundations
- Use level: 0.5—5.0% (w/w)

Solubility Data:

The following materials are soluble at 50% (w/w) in **Captex 300** at room temperature:

- Vitamin E Acetate
- Spanish Rosemary Oil
- Eucalyptus Oil
- Menthol

Hydrophilic/Lipohilic Balance:

The required HLB of **Captex 300** is 11, using surfactant blends of sorbitan laurate and Polysorbate 20.

Shelf-Life:

Retest and requalify 2 years from the date of manufacture.

Storage:

Store in a dry place at ambient temperature.

Standard Package:

Tank wagons, 425 lb. (193 kg) drums or 50 lb. (22.7 kg) pails

20 TH EDITION

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02 03 04
2 3 4 5 6 7 8 9 10

Table 23-1. Values of Modulus of Elasticity of Representative Solids at Room Temperature

MATERIAL	YOUNG'S MODULUS dyne/cm^2
Steel	2.2×10^{12}
Glass	6×10^{11}
Potassium chloride	2.3×10^{11}
Silk, viscose rayon	1.5×10^{11}
Microcrystalline cellulose	1.3×10^{11}
Polystyrene	3.4×10^{10}
Polyethylene (low density)	2.4×10^{9}
Rubber (vulcanized)	2×10^{7}
Tooth enamel	4.7×10^{11}
Bone	2.2×10^{11}
Tendon	1.3×10^{9}
Muscle	6×10^{6}
Soft tissue	7.5×10^{4}
Gelatin gels	
10% solids	2.4×10^{5}
20% solids	1.0×10^{6}
30% solids	1.5×10^{7}

law of proportionality between stress and strain is obeyed throughout the linear portion OL. The elastic modulus of the solid is the slope of OL or the tangent of the angle LOC. The material behaves elastically up to the yield point Y, where the stress is called *yield stress*. When stresses below the yield stress are applied to the sample and then released, it stretches and contracts along the same curve OLY.

Beyond Y, the material behaves as a plastic, rather than as an elastic solid. Along the (nearly) horizontal portion YAH, the material is ductile; it flows or creeps under practically constant stress like a viscous liquid. If the stress is released at A, the sample retracts along AC. The nonrecoverable deformation OC is called *permanent set*. Many materials undergoing such "cold flow" are strengthened by some change in structure, causing an upturn HB in the stress-strain curve. This is called work (or strain) hardening. It may result from the elimination of flaws,[1] from a reduction in crystal size as in the case of metals[2] or from reversible crystallization on stretching, as in the case of homopolymer elastomers.[3]

At B, the sample ruptures; R is the elongation at (or to) break or the ultimate elongation, and the stress corresponding to B is the ultimate strength or tensile strength. These values, as well as the load-elongation curve beyond Y, depend on the rate at which the sample is stretched.

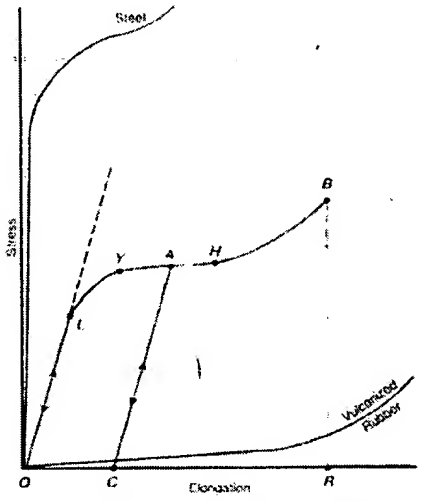

Figure 23-1. Stress-strain curves in tension. Loads or tensile stresses are corrected for actual cross-sectional areas.

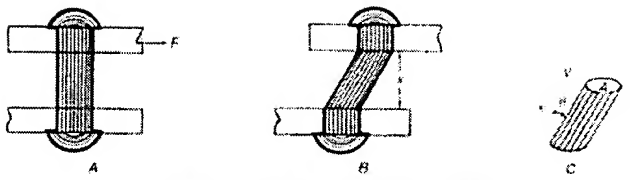

Figure 23-2. Effect of shear on a rivet.

The area $OLYAHBRCO$ under the stress-strain curve is the energy or work required to break or rupture the material. It measures its toughness or brittleness. Glass is hard because of its high elastic modulus. Owing to the absence of a yield point and to a very low elongation to break, it is brittle as opposed to steel, which undergoes work hardening, has a high elongation to break and is tough. Plastics are medium-hard or soft. Those which exhibit comparatively high elongations at break, like polyethylene but unlike polystyrene, are tough. Vulcanized rubbers are tough even though they are soft (low elastic modulus) because their elongation to break is very high, namely, 600 to 800%.

Liquids

Compressive stresses are the only kind of stresses which liquids can support and from which they recover. All other stresses produce infinite deformation if applied long enough, so that the elastic and shear moduli of liquids are zero.

Upon cutting a sheet of paper or of metal with scissors or shears, the deformation before severance is called *shear*. Pushing a deck of playing cards sideways is also deformation in shear. In Figure 23-2, the upper of the two metal plates held together by a rivet is pulled by a tangential force, F, while the lower plate is held stationary. *Shear stress*, τ, is F divided by the cross-sectional area A of the rivet parallel to the force. The *shear strain* or deformation in shear, γ, is the displacement y divided by the height, x, of the sheared or deformed portion of the rivet, as shown in Figure 23-2*C*. It equals the tangent of the displacement angle θ which, at low θ values, is approximately equal to θ expressed in radians.

$$\gamma = \frac{y}{x} = \tan \theta \cong \theta \qquad (2)$$

One can imagine a liquid contained between two very large, parallel plates as being divided into a stack of very thin, parallel layers much like a deck of cards, as shown in Figure 23-3. Shear is applied to the liquid by pulling or pushing the top plate with a constant force F while holding the bottom plate stationary. The velocities of the liquid layers are represented by the arrows in Figure 23-3, whose length measures the magnitude of the velocities and which point in the direction of flow (y-direction). The top liquid layer, in contact with the moving plate, adheres to it and moves with the same velocity as the

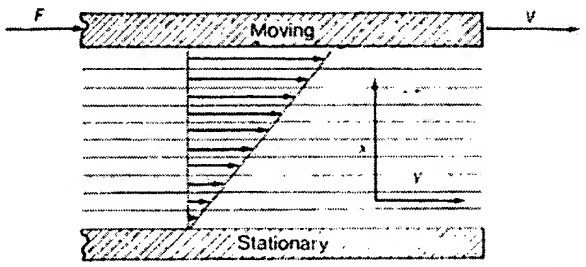

Figure 23-3. Laminar flow of a liquid contained between two parallel plates.

plate. The second layer, adjacent to the top one, is dragged along by friction, but its velocity is reduced somewhat by the resistance of the layers beneath it. Each layer is pulled forward by the layer moving above it but is held back by the layer underneath it, over which it moves and which it drags along. The farther the liquid layers are from the moving plate, the smaller their velocities. The bottom layer adheres to the stationary plate and has zero velocity. Thus, the velocity of the liquid layers increases in the direction x perpendicular to the direction of flow y.

In due time, all layers except the bottom one undergo infinite deformation. What distinguishes one liquid from another is the rate at which the deformation increases with time. This is called *rate of* (deformation in) *shear*. It is represented by $\dot{\gamma}$, which is the derivative of γ with respect to time, t. An equivalent definition for $\dot{\gamma}$ is as the *velocity gradient*, ie, the rate at which the velocity, v, changes with the distance, x, perpendicular to the direction of flow.

$$\dot{\gamma} = \frac{d\gamma}{dt} = \frac{dv}{dx} \tag{3}$$

The rate of shear or velocity gradient, $\dot{\gamma}$, indicates how fast the liquid flows when a shear stress is applied to it. Its unit according to both definitions is sec^{-1}, since γ is dimensionless, velocity is expressed in cm/sec and x in cm.

Equation 3 is illustrated by calculating the rate of shear when lotion is rubbed into the skin. If the hand (moving surface) slides across the skin (stationary surface) with a velocity $v = 45$ cm/sec and if the thickness of the lotion film is $x = 0.05$ cm, the rate of shear is $\dot{\gamma} = (45 \text{ cm/sec})/0.05 \text{ cm} = 900 \text{ sec}^{-1}$. For a given force and a constant viscosity, the rate of shear is uniform throughout the layer of lotion. Characteristic $\dot{\gamma}$ values for pharmacy-related operations are listed in Table 23-2. Even for a given operation, the shear rate can vary within wide limits, depending on the dimensions of the equipment and the speed at which it is operated.

The flow of liquids by parallel layers moving past each other and dragging adjacent layers along is called *laminar* or *streamline flow*. At higher velocities and/or if the plates have rough surfaces, eddies or swirls develop. This phenomenon is called *turbulent flow* and is described quantitatively in chemical engineering texts.

NEWTONIAN FLOW—Newton[2] observed that the shear stress, τ, or force F divided by the area A of the plate, is directly proportional to the rate of shear or velocity gradient. The proportionality constant is called (coefficient of) *viscosity*, η, while its reciprocal is called *fluidity*.

$$\tau = \frac{F}{A} = \eta\dot{\gamma} \tag{4}$$

Viscosity or internal friction is the resistance to the relative motion of adjacent layers of liquid. According to Eq 4, it is calculated as the ratio of shear stress to rate of shear. In the CGS system, viscosity is defined as the tangential force per unit area in dynes/cm^2 required to maintain a difference in velocity of 1 cm/sec between two parallel layers of liquid 1 cm apart. Its unit is therefore dynes/cm^2-sec^{-1} or g/cm-sec, which is called a *poise*. Because many common liquids including water have viscosities of the order of 1/100 of a poise, their viscosity is often expressed in *centipoises*. In the SI system, the unit of viscosity is Newton/m^2-sec^{-1} or Pascal sec, which equals 10 poise. Representative values are listed in Table 23-3.

Table 23-2. Approximate Shear Rate Levels for Pharmaceutical Operations

OPERATION	RATE OF SHEAR, sec^{-1}
Pouring from a bottle	50
Spreading lotion on skin, levigating ointment on slab with spatula	400–1000
Injecting through hypodermic syringe	4000
Dispensing nasal spray from plastic squeeze bottle	20,000
Processing in colloid mill	10^3–10^5

Table 23-3. Newtonian Viscosities and Activation Energies for Viscous Flow[a]

MATERIAL	TEMPERATURE, °C	VISCOSITY, POISE	ACTIVATION ENERGY FOR VISCOUS FLOW, kcal/mole
Water	20	0.0100	4.2
	50	0.0055	3.4
	99	0.0028	2.8
Ethanol:			
absolute	20	0.0120	3.3
	50	0.0070	3.3
40% *w/w*	20	0.0291	6.8
	50	0.0113	5.3
Benzene	20	0.0065	2.5
	50	0.0044	2.5
Ethyl ether	20	0.0024	1.65
Glycerin:			
anhydrous	20	15.00	12.5
95% *w/w*	20	5.45	10.6
Castor oil	20	10.3	13.2

[a] At 1 atm pressure.

Flow through cylindrical pipes or capillaries is laminar at low velocities and/or for small tube radii and/or viscous liquids. The liquid layers are very thin cylinders concentric with the duct.[2] During flow, they telescope past one another as shown in Figure 23-4*A*.[10] The arrows in Figure 23-4*B* represent the velocity v of the individual cylindrical layers of radius r; v is maximum in the center of the tube and decreases in the radial direction, ie, in the direction r (previously x) perpendicular to the direction of flow y. The velocity is zero in the outermost liquid layer adjacent and adhering to the wall, whose radius is equal to the inside radius of the tube R. In the center of the tube, where v is maximum, the velocity gradient $dv/dr = \dot{\gamma}$ is zero. This is shown in Figure 23-4*C*, where the arrows represent $\dot{\gamma}$ and the velocity gradient is maximum at the wall.

If V is the volume of liquid flowing through a cylindrical tube of radius R in time t, the volumetric flow rate is V/t, and the shear rate at the wall is

$$\dot{\gamma}_{r=R} = \frac{4}{\pi R^3}\left(\frac{V}{t}\right) \tag{5}$$

The shear stress is zero in the center of the tube and maximum at the wall.

$$\tau_{r=R} = \frac{R\Delta P}{2L} \tag{6}$$

The liquid is made to flow through the tube by pressure, either caused by its own weight (hydrostatic) or produced by a pump. This pressure is used to overcome the viscous friction of the liquid, and is converted into heat. The pressure drop along a length L of tube, ΔP, is the difference in the pressure at the beginning and at the end of that length.

Viscosity is shear stress divided by rate of shear. Since both vary in the x-direction perpendicular to the direction of flow, both must be taken at the same location. Using the values at the wall of a cylindrical tube, dividing Eq 6 by Eq 5 and rearranging gives

$$\frac{V}{t} = \frac{\pi R^4 \Delta P}{8L\eta} \tag{7}$$

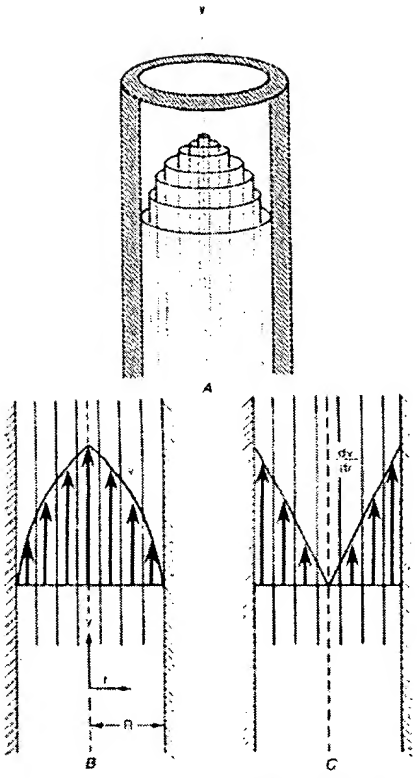

Figure 23-4. Laminar flow of a liquid through a cylindrical duct. *A*: Three-dimensional view of telescoping layers;[10] *B*: cross-section showing radial distribution of velocity; *C*: cross-section showing radial distribution of velocity gradient.

This is *Poiseuille's law*, found experimentally by this French physician while studying the flow of liquids through capillary tubes representative of blood vessels. The poise is also named in his honor. In the CGS system, pressure is expressed in dynes/cm^2 and V/t in cm^3/sec; 10 dynes/cm^2 equals 1 Newton/m^2, or Pascal.

In the human body, the pumping action of the heart supplies the driving pressure for the flow of blood, which is the difference between the arterial and venous pressure.[11] Digitalis increases the force of contraction of the heart muscle and makes the heart a more efficient pump. This increases ΔP and, hence, the rate of flow of blood V/t. Vasodilator drugs like nitroglycerin or hydralazine hydrochloride increase the radius of blood vessels by relaxing the vascular smooth muscles. Since the flow rate varies with the fourth power of the radius of the blood vessel, a mere 5% increase in radius causes a 22% increase in the flow rate at constant blood pressure, because $(1.05)^4 = 1.22$.

The viscosity of simple liquids, ie, pure liquids consisting of small molecules and solutions where solute and solvent are small molecules, depends only on composition, temperature and pressure. It increases slowly with increasing pressure and fast with decreasing temperature. For solutions of solid solutes, the viscosity usually increases with concentration. Simple liquids follow Newton's law (Eq 4) of direct proportionality between shear stress and rate of shear, so that their viscosity does not depend on either. This is called *Newtonian flow behavior*. The liquids listed in Table 23-3 and their viscosities are Newtonian.

The flow curves or consistency curves of Newtonian liquids, like those of Figure 23-5, are straight lines going through the origin. Viscosity is the slope of such a line or the tangent of the angle it makes with the horizontal axis. Of the two liquids shown in Figure 23-5, *A* has a higher viscosity than *B* because $\alpha > \beta$, so that $\eta_A = \tan\alpha > \eta_B = \tan\beta$; $\eta_A = \tau_2/\dot{\gamma}_2 = \tau_1/\dot{\gamma}_1$ and $\eta_B = \tau_1/\dot{\gamma}_1 = \tau_2/\dot{\gamma}_2$. A given shear stress, τ_1, produces a greater rate of shear, $\dot{\gamma}_2$, in the more fluid Liquid *B* than $\dot{\gamma}_1$ in the more viscous Liquid *A*. Alternatively, to produce a given rate of shear, $\dot{\gamma}_2$, in the two liquids requires a higher shear stress, τ_2, for the more viscous Liquid *A* than τ_1 for the more fluid Liquid *B*. Some texts plot consistency curves with shear stress on the horizontal axis and rate of shear on the vertical axis.[12] The slope of those plots represents fluidity; viscosity is the reciprocal slope.

The variation of viscosity with temperature often is described by an *Arrhenius equation*:

$$\eta = Ae^{E/RT}$$

or

$$\ln \eta = \ln A + E/RT \qquad (8)$$

where A and E are constants, T is the absolute temperature and R is the gas constant. Values of E, the *activation energy* for viscous flow, are listed in Table 23-3. Large values of E indicate that the viscosity decreases fast with rising temperature. According to Eq 8, plots of ln η versus the reciprocal of the absolute temperature should be straight lines with slopes of E/R. For associated, eg, hydrogen-bonded, liquids such plots are often somewhat curved.

According to the "*hole theory*," liquids contain vacancies or holes which are essential to flow. The activation energy is used largely to form these holes.[13] E is about $\frac{1}{4}$ to $\frac{1}{3}$ of the latent heat of vaporization for nonassociated liquids.

TIME-INDEPENDENT NON-NEWTONIAN BEHAVIOR—*Pseudoplasticity*—Many colloidal systems, especially polymer solutions and flocculated solid/liquid dispersions, become more fluid the faster they are stirred. This shear-thinning behavior is called *pseudoplasticity*.[6,8,9,11,12] It is an example of non-Newtonian flow behavior because the viscosity is not constant (at constant temperature and composition) as required by Newton's law of viscous flow (Eq 4), but decreases with increasing shear. The shear rate increases faster than the shear stress, making the flow curve of Figure 23-6 concave towards the shear-rate axis.

There is an apparent viscosity for each value of shear rate or shear stress, which can be expressed in two different ways. At point P in Figure 23-6, the apparent viscosity can be taken as the slope of the secant to the flow curve at P, or $\tan\theta$, which is the viscosity of a Newtonian liquid whose flow curve passes through P.[6,14] This is equal to the ratio $\tau_P/\dot{\gamma}_P$.[8,9] The second method[15] defines the apparent viscosity as the slope of the tangent to the flow curve at P, ie, $d\tau_P/d\dot{\gamma}_P = \tan\phi$. Since both θ and ϕ decrease with increasing shear stress or shear rate, so does the viscosity.

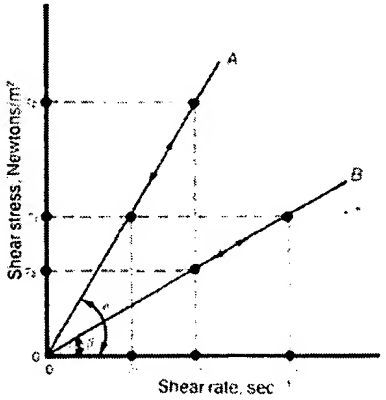

Figure 23-5. Consistency or flow curves of two Newtonian liquids.

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Twelfth Edition

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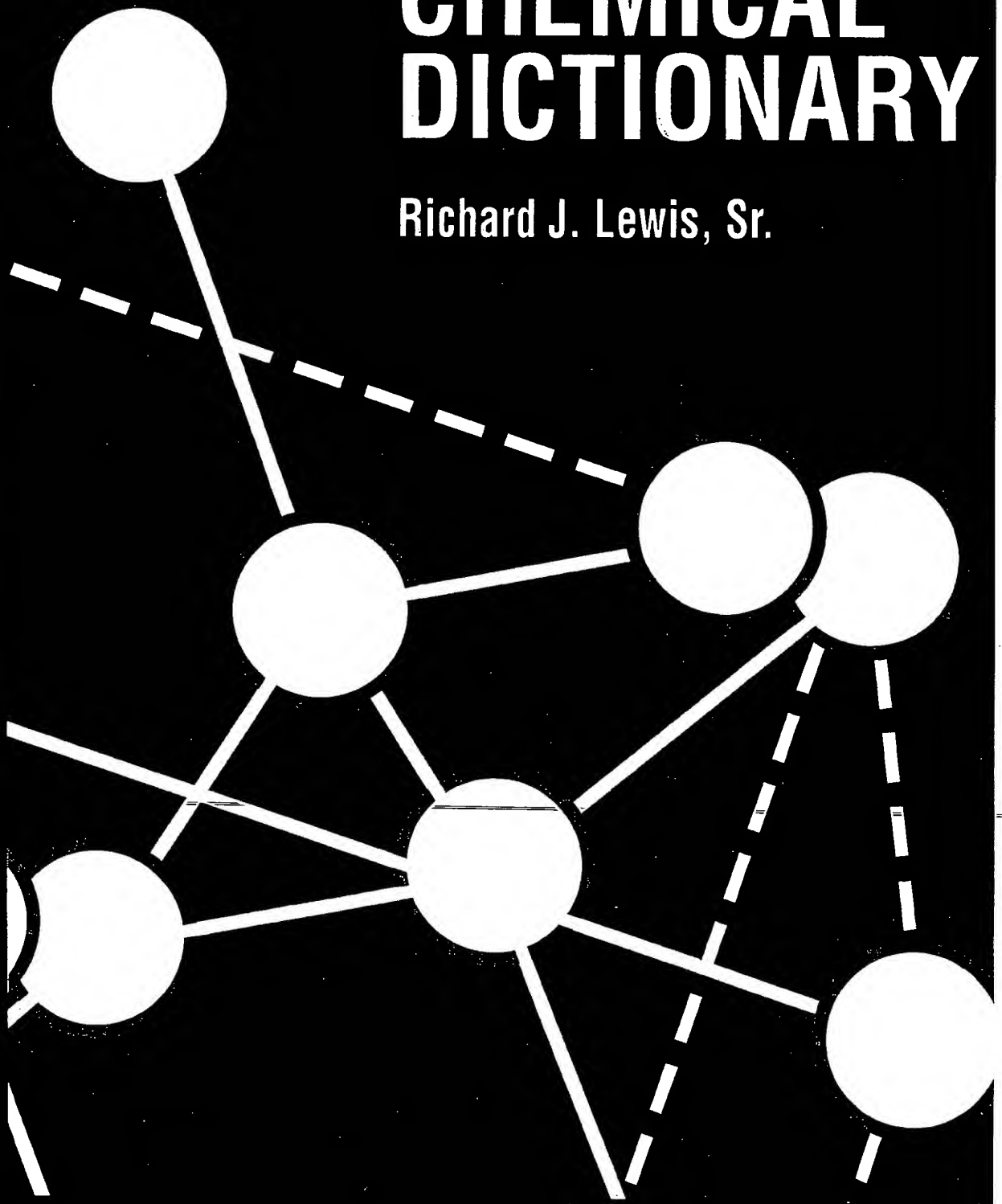

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Dictionary

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that are resistant to other antibiotics. Available commercially as sulfate.

viosterol. Irradiated ergosterol.

Virtanen, Arrturi I. (1895–1973). A Finnish biochemist who won the Nobel prize in 1945. His work was primarily concerned with research in nutrition and agriculture. He made important discoveries regarding prevention of fodder spoilage and bacterial fermentation as well as nitrogen metabolism in plants. His PhD was awarded at the University of Helsinki, followed by an illustrious career that included awards throughout Scandanavia.

virus. An infectious agent composed almost entirely of protein and nucleic acids (nucleoprotein). Viruses can reproduce only within living cells and are so small that they can be resolved only with an electron microscope. Because they pass through filters that retain bacteria, they are often called filterable viruses. Tobacco mosaic was the first virus to be crystallized and isolated (Dr. W. M. Stanley, 1935); it contains some 2000 protein molecules in a sequence of 158 amino acids (molecular wight 40,000,000). Bushy stunt virus found in tomato plants has a molecular weight of 7,600,000. First synthesis of a virus was reported in 1967.

Viruses differ from organisms in that they are only half alive; they lack metabolism, are unable to utilize oxygen, to synthesize macromolecules, to grow, or to die. They are parasites, relying on a living host cell. They account for many diseases, including mumps, measles, scarlet fever, smallpox, influenza, and possibly the common cold. Their shapes are similar to those of bacteria (rods, spheres, filaments). They have the ability to mutate; they are also antigenic and, thus, initiate formation of antibodies. Some act as bacteriophages. A direct relation between virus and cancer has been shown, the DNA of the virus becoming irreversibly bound to the DNA of the affected cells.

See also bacteria, deoxyribonucleic acid.

viscometer. (viscosimeter). A device for measuring the viscosity of a liquid. The types most widely used are the Engler, Saybolt, and Redwood, which indicate viscosity by the rate of flow of the test liquid through an orifice of standard diameter or the flow rate of a metal ball through a column of the liquid; other types utilize the speed of a rotating spindle or vane immersed in the test liquid. The liquids commonly measured are lubricating oils and the like; heavier (non-Newtonian) liquids such as paints and paper coatings require more complex devices, e.g., Brookfield and Krebs-Stormer.

See also viscosity.

viscose process. The best-known process for making regenerated cellulose (rayon) by converting cellulose to the soluble xanthate, which can be spun into fibers and then reconverted to cellulose by treatment with acid. Wood pulp is steeped with 17–20% caustic soda; the resulting alkali cellulose is pressed to remove excess liquor and the soluble β- and γ-cellulose, and then shredded and aged. It is then treated with carbon disulfide and sodium hydroxide to form an orange, viscous solution of cellulose xanthate. After filtration and deaeration, this solution (viscose) is forced through minute spinneret openings (or long slit dies in the case of cellophane) into a bath containing sulfuric acid and various salts such as sodium and zinc sulfate. The salts cause the viscose to gel immediately, forming a fiber or film of sufficient strength to permit it to be drawn through the bath under tension. At the same time, the sulfuric acid decomposes the xanthate, converting the fibers to cellulose, in which form they are washed and dried.

See also rayon, cellophane.

viscosimeter. See viscometer.

viscosity. The internal resistance to flow exhibited by a fluid, the ratio of shearing stress to rate of shear. A liquid has a viscosity of one poise if a force of 1 dyne/square centimeter causes two parallel liquid surfaces one square centimeter in area and one centimeter apart to move past one another at a velocity of 1 cm/s. One poise equals 100 centipoises. Viscosity in centipoises divided by the liquid density at the same temperature gives kinematic viscosity in centistokes (cs). One hundred centistokes equal one stoke. To determine kinematic viscosity, the time is measured for an exact quantity of liquid to flow by gravity through a standard capillary.

Water is the primary viscosity standard with an accepted viscosity at 20C of 0.01002 poise. Hydrocarbon liquids such as hexane are less viscous. Molasses may have a viscosity of several hundred centistokes, while for a very heavy lubrication oil, the viscosity may be 100 centistokes. There are many empirical methods for measuring viscosity.

See Saybolt University Viscosity; viscometer.

viscosity index improver. A lubricating oil additive that has the effect of increasing the viscosity of the oil in such a way that it is greater at high temperature than at low temperature. Agents used for this purpose are polymers of alkyl esters of methacrylic acid, polyisobutylenes, etc.

viscosity, kinematic. See viscosity.

"Vistac A" [*AKZO*]. TM for a series of synthetic hydrocarbon polymers.

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date below:

September 28, 2005 — Michael C. Barrett
Date — Michael C. Barrett

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Mumper & Jay

Serial No.: 09/812,884

Filed: March 21, 2001

For: Microemulsions as Precursors to Solid Nanoparticles

Group Art Unit: 1615

Examiner: Micah Paul Young

Atty. Dkt. No.: NANO:003US

Declaration of Dr. Russell Mumper under 37 C.F.R. §1.132

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P.O. Box 1450
Alexandria, VA 22313-1450

I, Russell Mumper, declare that:

1. I am a citizen of the United States residing at 4804 Hempstead Drive, Lexington, Kentucky, 40515. I am a faculty member at The University of Kentucky, College of Pharmacy. I am an inventor of the present patent application. This declaration is based on my personal knowledge.

2. I understand that the Patent Office has alleged that the present application does not adequately disclose a process by which a solid nanoparticle is obtained. I understand that the Patent Office alleges that the practice of the invention should result in a non-solid product.

3. I am submitting this declaration to demonstrate that when exemplary procedures of the present application are followed consistent with the language of the claimed invention, solid nanoparticles are formed.

4. Attached behind Tab A of this Declaration are results from experiments I conducted, showing the formation of solid nanoparticles made in accordance with exemplary techniques consistent with the language of the claimed invention. The results include seven figures (Figures 1-7). Figure 1 shows the thermal analysis of nanoparticle components and nanoparticles using Differential Scanning Calorimetry (DSC). Figure 2 is an image of the nanoparticles using a Transmission Electron Microscope (TEM). Figures 3-7 are images of the nanoparticles taken using a high resolution field emission Scanning-Transmission Electron Microscope (STEM) operating in both TEM and STEM mode. This type of STEM imaging uses z-contrast and creates an imaging signal that is proportional to the atomic number squared in the ideal case. An Energy Dispersive X-ray Spectroscopy (EDS) profile is also included in Figure 7. The STEM/EDS technique allows one to scan into a solid material and determine where an element is located.

5. Turning to the figures of Tab A, it is evident that the pictured nanoparticles are solid for at least three reasons. First, the DSC profile of the nanoparticles (Figure 1.3) shows a single endothermic peak at ~ 90° C demonstrating that the nanoparticles have a distinct and unique melting point and are therefore a solid. Second, the TEM methods that were used to generate Figures 2-7 required the nanoparticle suspension to be dried (water removed) on a substrate for suitable for TEM analysis. After drying, distinct solid nanoparticles are observed (Figures 2-7). In contrast, the drying of an oil-in-water microemulsion (a liquid-in-liquid) would result in a heterogeneous mass of coalesced oil deposited on the substrate. In fact, for such a

liquid system, Freeze-Fracture TEM (FF-TEM) would have to be employed to first freeze the system using low temperatures so that distortions associated with the removal of water can be avoided. FF-TEM was not required for the imaging of the pictured nanoparticles because they are solid. Third, as shown by X-ray Spectroscopy, Holmium (an element I incorporated in the nanoparticles) is uniformly present in the pictured nanoparticle in a punctate manner. (Figures 4-7). The Energy Dispersive X-ray Spectroscopy profile in Figure 7 illustrates that Holmium is present uniformly throughout the solid nanoparticle when the nanoparticle is scanned along its diameter.

6. The solid nanoparticles were made in accordance with exemplary techniques consistent with the language of Claim 21 and described at pages 20-21 of the specification and in Examples 6, 8, 9, and 13 of the specification (found at pages 30-33 and 35).

7. For Figure 1, the solid nanoparticles were made by first melting emulsifying wax at 55° C. Seven hundred µL of water was added into the melted wax and stirred using a magnetic mixer until a homogenous milky suspension was obtained. Then, 0.3 mL of cetyltrimethyl ammonium bromide (CTAB) solution (50 mM) was added into the homogenate while stirring to obtain a clear microemulsion at 55° C. Solid nanoparticles were then formed by cooling this warm microemulsion to room temperature, while stirring, in the same container.

8. For Figure 2, the solid nanoparticles were made by weighing 2 mg of emulsifying wax into a 7-mL screwed capped glass vial. The emulsifying wax was melted at 55° C. To the melted emulsifying wax, 30 µL of 100 mM Brij 78 surfactant solution was added. Next, water was added under magnetic stirring to prepare the oil-in-water microemulsion at 55° C with a final volume of 1000 µl. Finally, solid nanoparticles were prepared directly from the warm

microemulsion by cooling of the undiluted oil-in-water microemulsion at 55° C to room temperature, while stirring.

9. For Figures 3-7, the solid nanoparticles were made using the following method. In a 7-mL glass vial containing a 1 cm magnetic stir bar, two (2) milligrams of emulsifying wax was melted at 65° C to produce a liquid nanoparticle matrix material. Next, 4.6 mg of Brij 78 surfactant was added. Next, 0.5 mg Holmium-acetylacetonate (Ho-AcAc) was dissolved into the melted mixture of emulsifying wax and Brij 78. One mL of water was added, and the mixture was heated for 15 minutes at 65° C while stirring with a magnetic mixer to make an oil-in-water microemulsion. Finally, the oil-in-water microemulsion was then cooled to room temperature while stirring to form a solid nanoparticle with entrapped Ho-AcAc.

10. It is evident that when nanoparticles are made according to exemplary techniques described in the present application and consistent with the language of the claimed invention, those nanoparticles are solid.

11. All statements made of my knowledge are true, and all statements made on information and belief are believed to be true, and these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the referenced patent application or any patent issued on it.

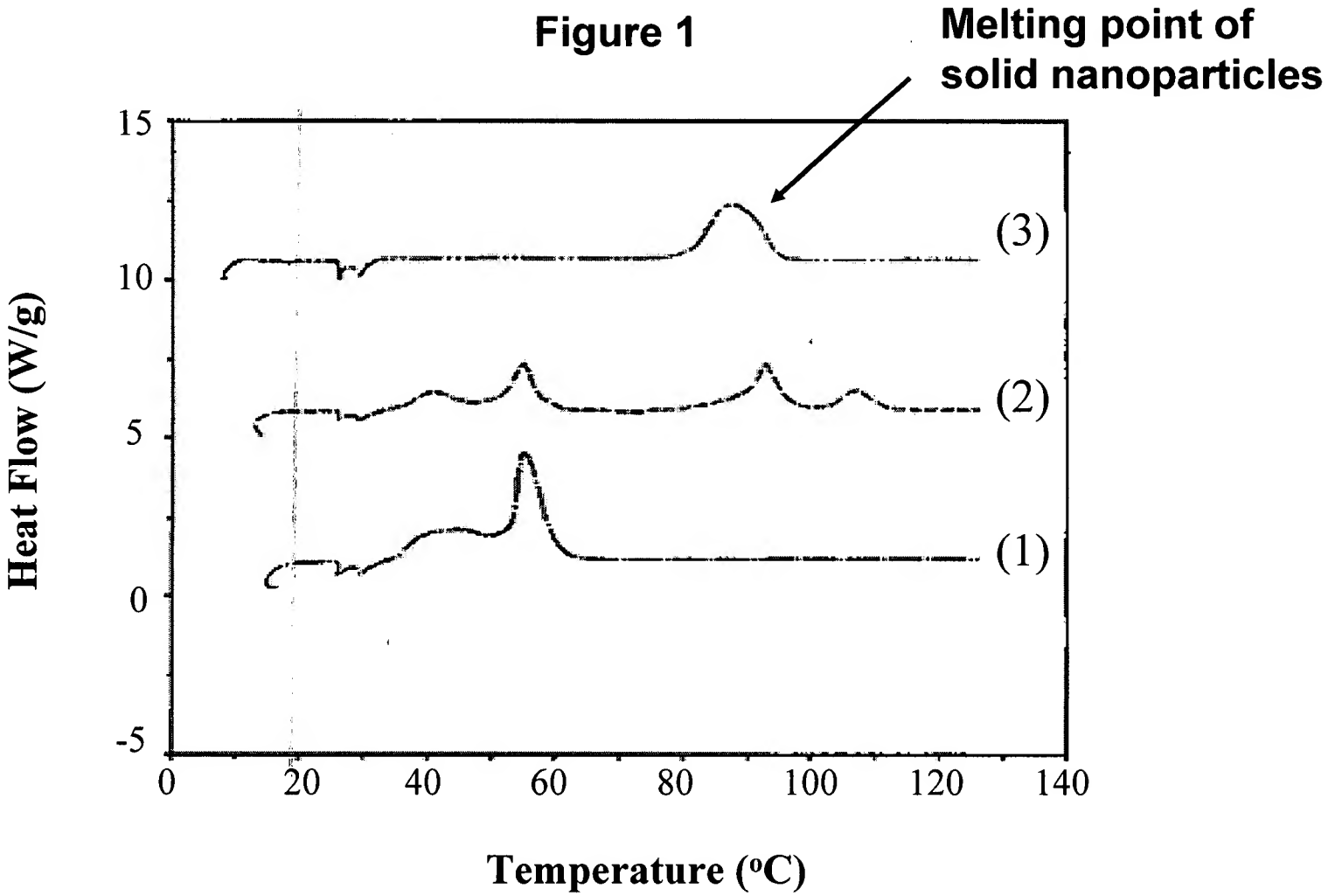
9-28-05

Date

Russell J Mumper

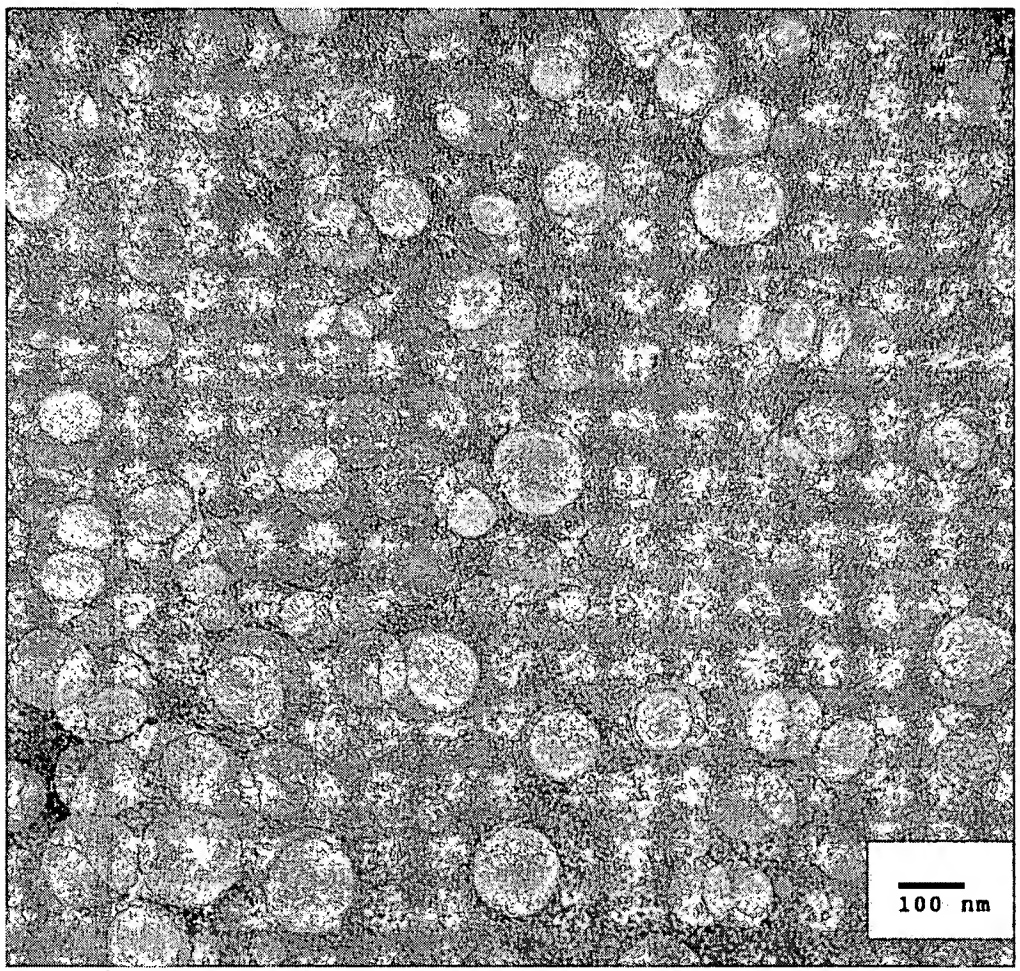
Russell Mumper, Ph.D.

Figure 1



DSC profiles of emulsifying wax (**1**), physical mixture of the CTAB surfactant and emulsifying wax (**2**), and the lyophilized nanoparticles (**3**). The nanoparticles were engineered from microemulsion precursors comprised of CTAB (15 mM) and emulsifying wax (2 mg/mL). For **2** and **3**, the ratios (w/w) of the emulsifying wax and CTAB were the same. The melting point of CTAB was reported to be 230°C.

Figure 2



Transmission Electron Micrograph of Solid Nanoparticles

STEM/EDS Analysis of NPs

- The images on the following slides were taken using a high resolution field emission Scanning-Transmission Electron Microscope (STEM) operating in both TEM and STEM mode. An Energy Dispersive X-ray Spectroscopy (EDS) profile is included.
- This type of STEM imaging used z-contrast and creates an imaging signal that is proportional to the atomic number squared in the ideal case.
- The solid NPs were made entrapping Holmium Acetylacetonate in the NPs. STEM/EDS allows one to scan through the nanoparticle and determine the Holmium distribution within the particle.

Two conclusions can be drawn from these pictures:

1) the NPs are solid
2) Ho is dispersed evenly throughout the solid NP

Figure 3

TEM image
(dark contrast)

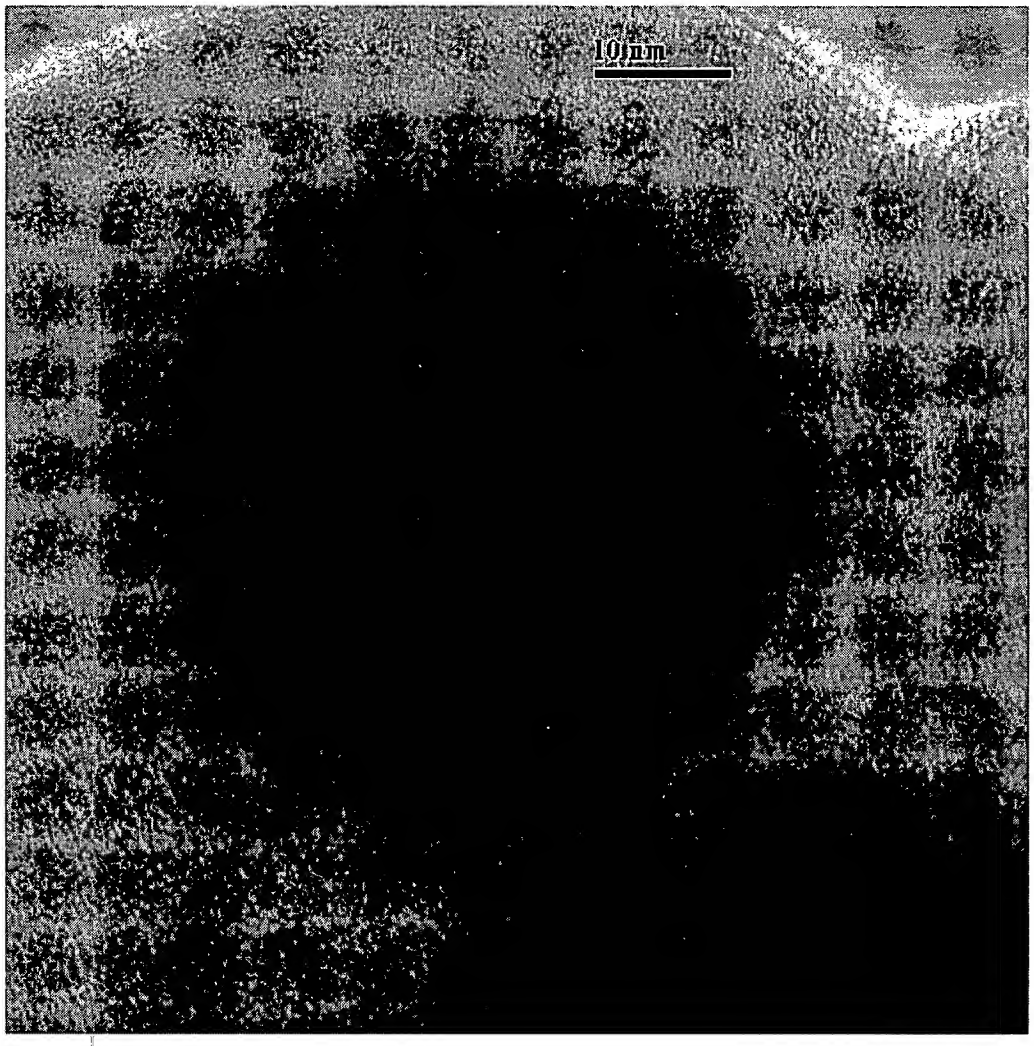
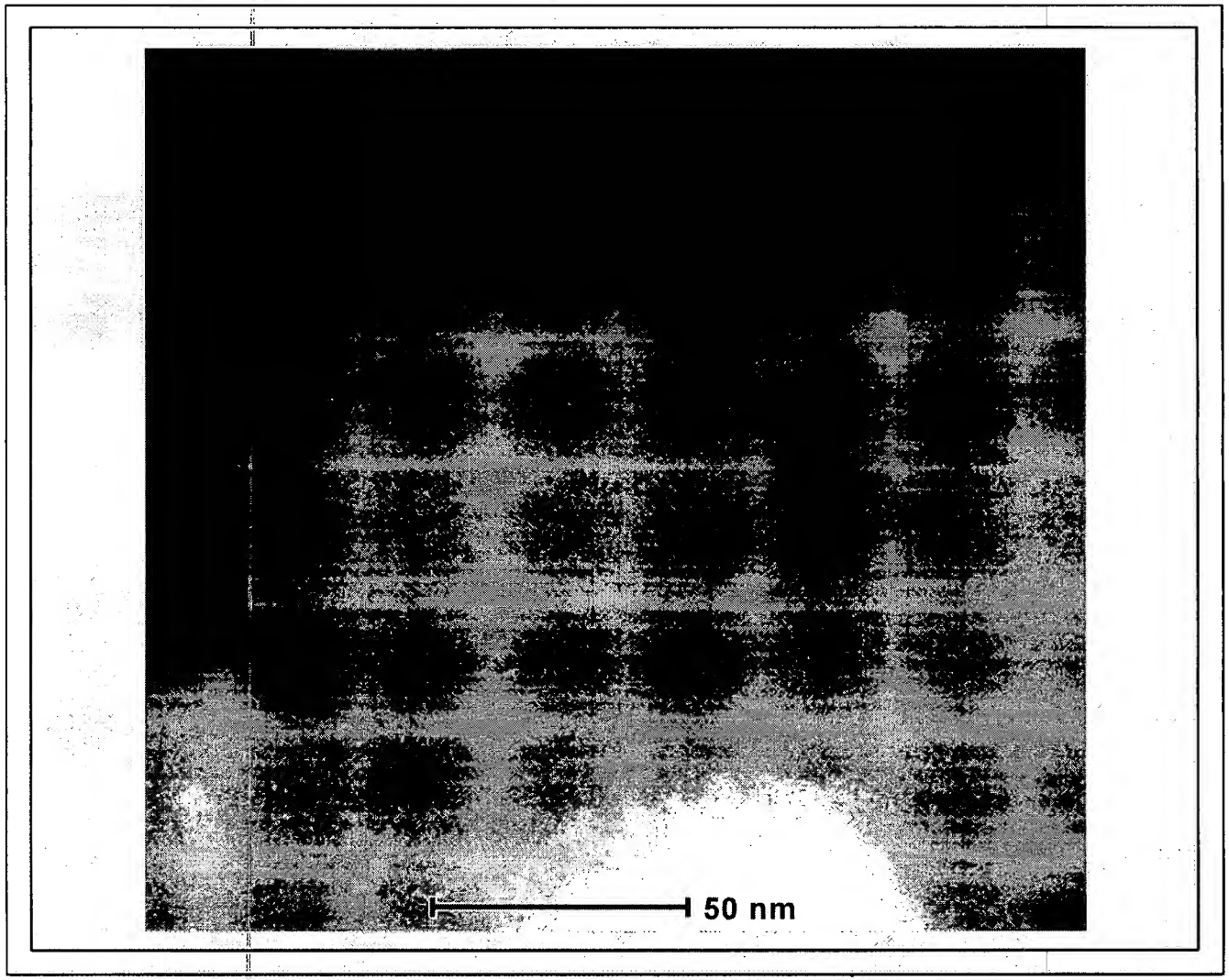


Figure 4



STEM image (light contrast)

Figure 5

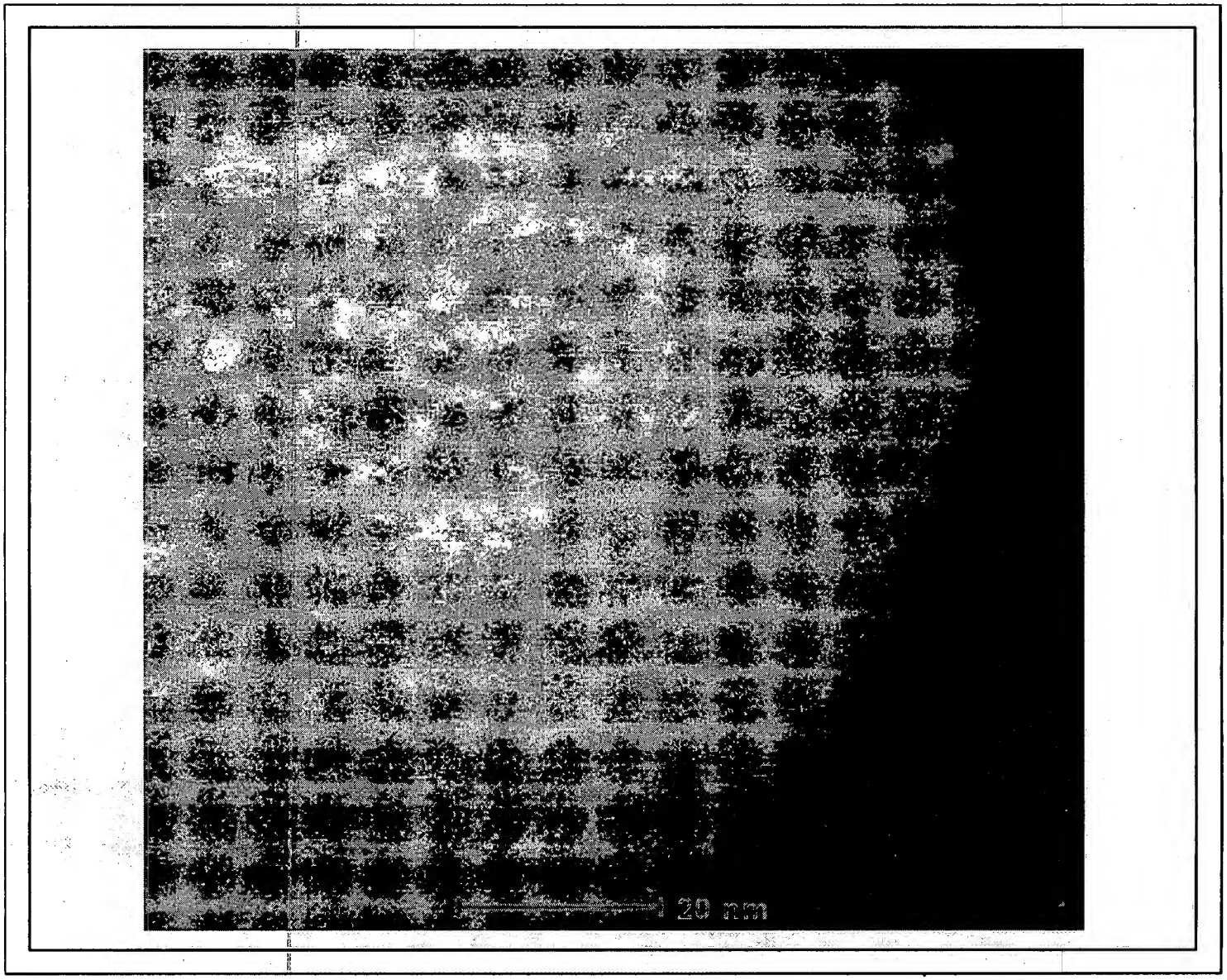


Figure 6

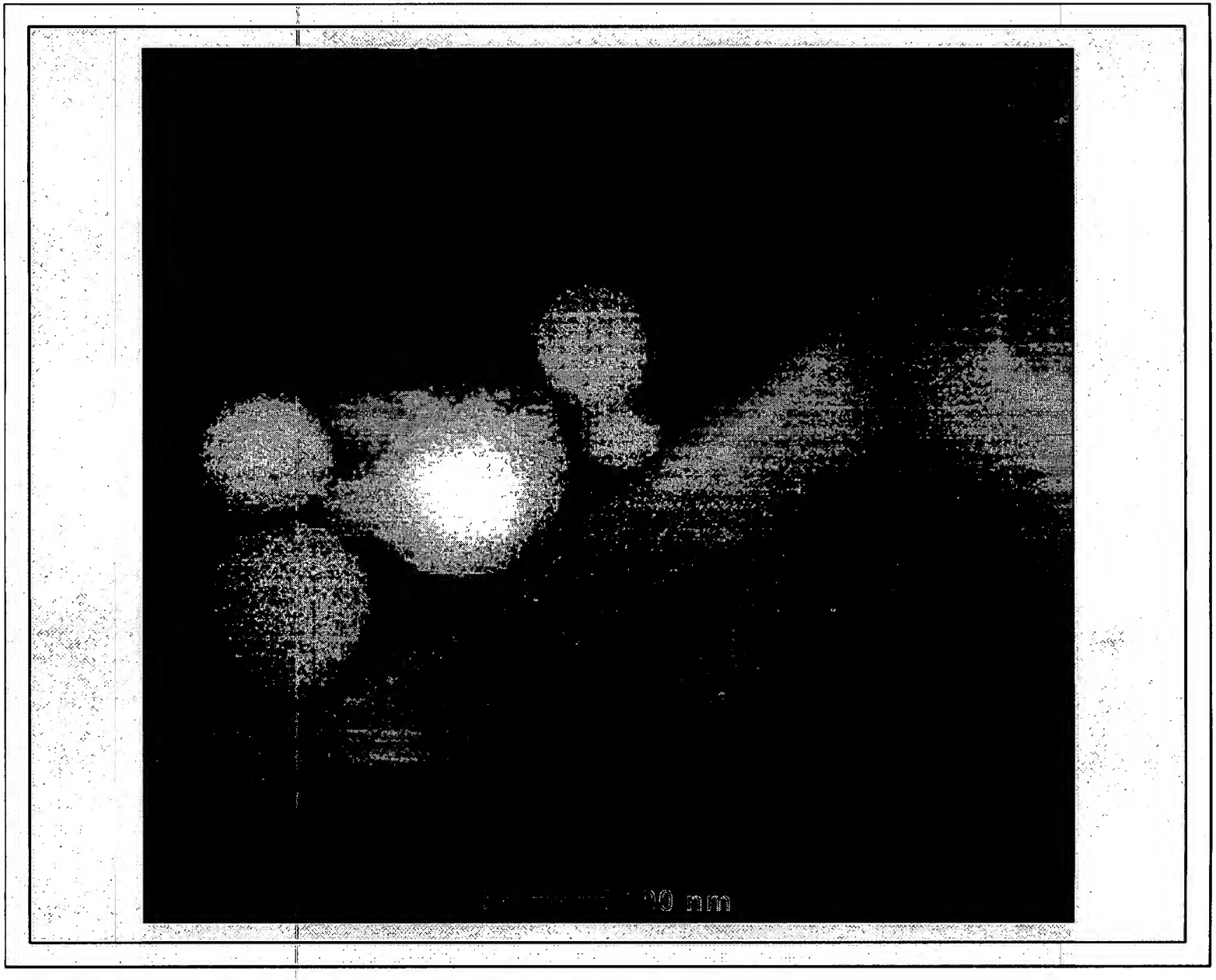
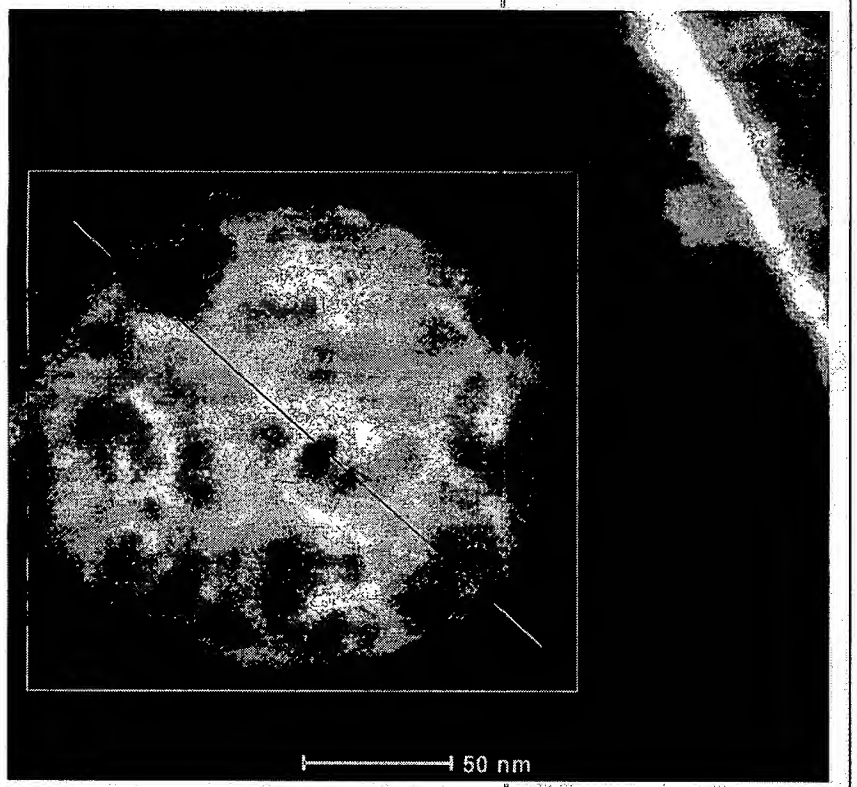


Figure 7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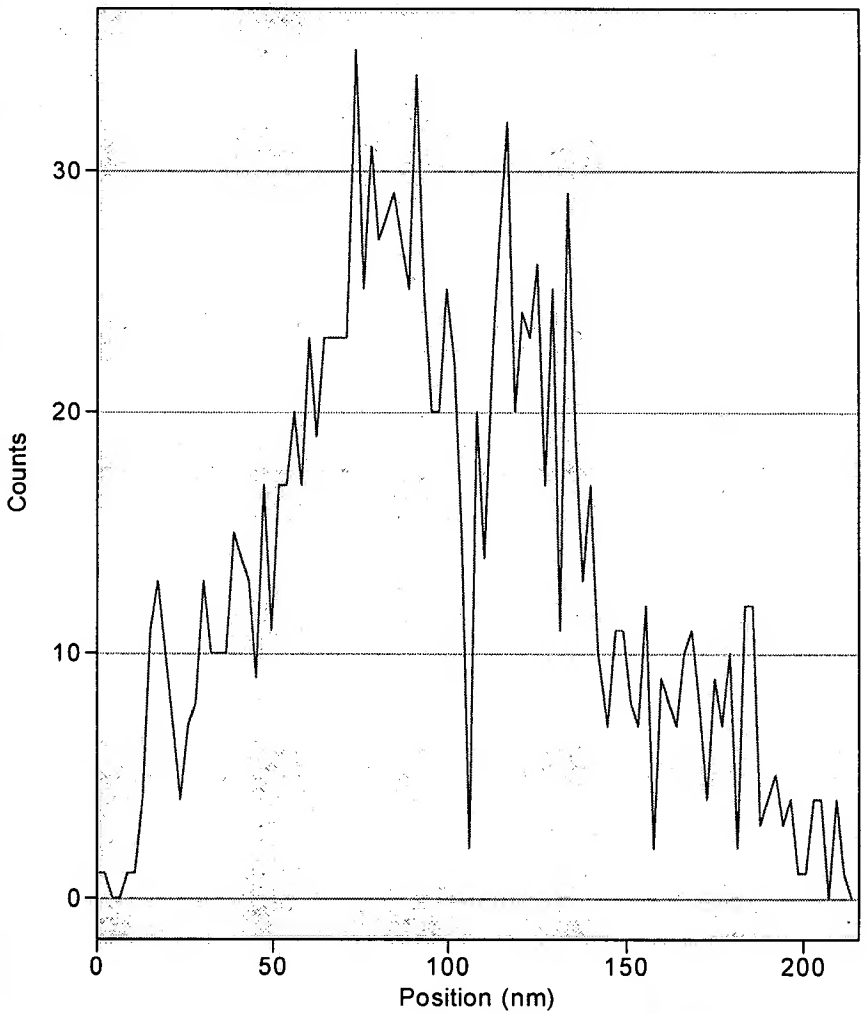
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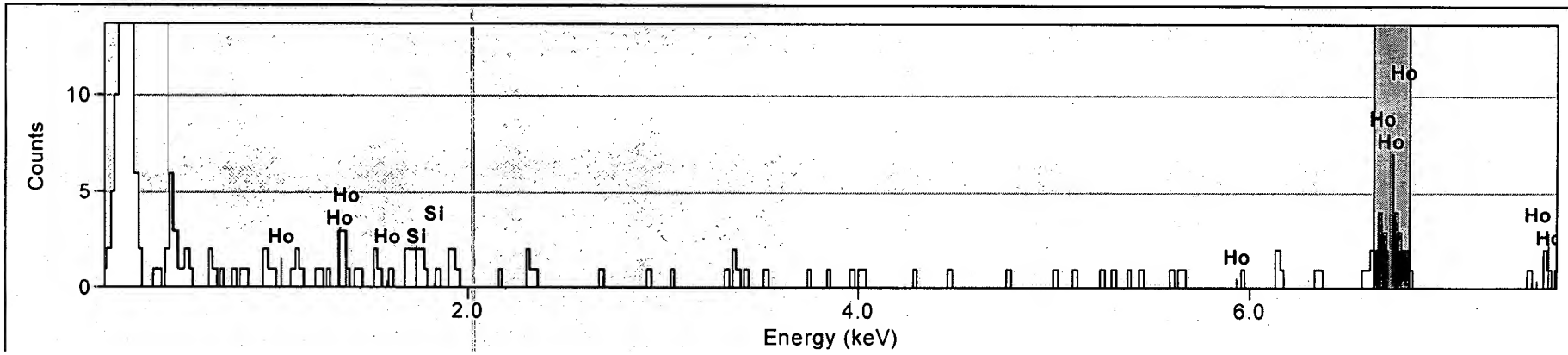
Position (nm)


Counts
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Energy (keV)